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(71) Applicant *(for all designated States except US)*: **BIOCURE, INC.** [—/US]; Suite 100, 2975 Gateway Drive, Norcross, GA (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CHAOUK, Hassan** [AU/US]; 1331 Lincoln Court Avenue, Atlanta, GA 30329 (US). **HOLLAND, Troy** [US/US]; 2775 Northcliff Drive, Suwanee, GA 30024 (US). **ASFAW, Bruktawit, T.** [ET/US]; 324 Windmont Drive, Atlanta, GA 30329 (US). **GOODRICH, Stephen, D.** [US/US]; 7990 East Snyder Road #7106, Tucson, AZ 85750 (US).

(74) Agent: **BEARD, Collen, A.**; BioCure, Inc., Suite 100, 2975 Gateway Drive, Norcross, GA 30071 (US).

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(54) Title: COMPOSITIONS FOR DRUG DELIVERY

(57) Abstract: Compositions comprising macromers having a blackbone comprising a polymeric backbone comprising units with a 1,2-diol or 1,3-diol structure, such as polyvinyl alcohol, and pendant chains bearing crosslinkable groups and, optionally, other modifiers. The composition includes an active agent or the active agent is added during administration of the composition. When crosslinked, the macromers form hydrogels having many properties advantageous for use as agents for drug delivery.

COMPOSITIONS FOR DRUG DELIVERY

Background of the Invention

The invention relates to compositions for use in drug delivery and to methods for drug delivery. More specifically, the invention relates to compositions including crosslinkable macromonomers (referred to herein as macromers) that form hydrogels useful in drug delivery and methods of using these compositions for drug delivery.

Drug delivery devices have historically been solid dosage forms. It is often desirable to have sustained delivery of an active agent from the dosage form at a specific site. Accordingly, implantable dosage forms have been developed. Many of these dosage forms require the surgical implantation of the solid dosage form. Drug delivery devices have been developed that include an in situ formed hydrogel. Generally, such devices include one of three types of polymer systems- thermosensitive compositions that solidify at body temperature; precipitating polymers that solidify when the solvent in which they are administered is washed away by the body's aqueous fluids; and macromer based systems, in which two or more macromers polymerize in situ to form a crosslinked polymer.

For example, U.S. Patent No. 5,410,016 to Hubbell et al. discloses hydrogels useful for drug delivery made from photopolymerizable macromers having a biodegradable region, preferably hydrolyzable under in vivo conditions, a water soluble region (preferably polyethylene glycol), and at least two polymerizable regions.

U.S. Patent No. 6,166,130 to Rhee et al. discloses crosslinked polymer compositions formed from a first synthetic polymer containing multiple nucleophilic groups crosslinked using a second synthetic polymer containing multiple electrophilic groups, allegedly useful for drug delivery.

U.S. Patent No. 6,201,072 to Rathi et al. discloses thermosensitive biodegradable triblock polymers based on biodegradable polyester and polyethylene glycol(PEG) blocks. The polymers exist as clear solutions at, or about, 5 °C to 25 °C in water but, when the temperature is raised to about body temperature (typically 37 °C for humans), they spontaneously interact to form semisolid hydrogels.

Atrix Laboratories has developed the Atrigel drug delivery system, which is based on a biodegradable polymer that can be presented as a liquid, gel, paste, or putty. This polymer solidifies when it comes into contact with body fluids, and forms a biodegradable implant that can be used for drug delivery.

Summary of the Invention

The invention relates to compositions for drug delivery comprising macromers having a backbone of a polymer containing units with a 1,2-diol and/or 1,3-diol structure. Such polymers include polyvinyl alcohol (PVA) and hydrolyzed copolymers of vinyl acetate, for example, copolymers with vinyl chloride, N-vinylpyrrolidone, etc. The backbone polymer contains pendant chains bearing crosslinkable groups and, optionally, other modifiers. When crosslinked, the macromers form hydrogels advantageous for use in drug delivery.

The invention also relates to methods for drug delivery wherein the compositions described above are formed into a hydrogel *in situ,* which releases a drug over a period of time. The drug can be formulated into the hydrogel in a number of ways.

In one embodiment, the compositions form a permanent implant. In another embodiment, the compositions form a temporary or reversible (the terms temporary and reversible are herein used interchangeably) implant. Temporary implants can be formed by using a fully or partially degradable composition or a composition that degrades in response to an applied condition, such as a change in temperature or pH.

The methods for using the compositions as in situ forming drug delivery devices include the step of delivering the macromers to the intended site using a delivery device such as a catheter or syringe. The macromers are then crosslinked into a hydrogel, generally upon exposure to a crosslinking initiator. In one embodiment, the macromers are dissolved in a biocompatible solution prior to administration. In one embodiment, the macromers are exposed to the crosslinking initiator before they are administered to the intended site.

Detailed Description of the Invention

The invention relates to compositions for use in drug delivery comprising macromers having a backbone of a polymer containing units with a 1,2-diol and/or 1,3-diol structure and having at least two pendant chains including a crosslinkable group, and optionally, pendant chains containing modifiers. The macromers form a hydrogel when crosslinked. In one embodiment, the macromers are exposed to a polymerization initiator upon or after administration to the intended site. In another embodiment, the macromers are exposed to the initiator prior to delivery and complete crosslinking is delayed until the composition is in place.

The compositions can be produced very simply and efficiently due to a number of factors. Firstly, the starting materials, such as polyhydroxy polymer backbones, are inexpensive to obtain or prepare. Secondly, the macromers are stable, so that they can be subjected to very substantial purification. The crosslinking can therefore be carried out using a macromer that is

highly pure, containing substantially no unpolymerized constituents. Furthermore, the crosslinking can be carried out in purely aqueous solutions. Aldehyde is not required.

I. The Compositions

The Macromer Backbone

The macromers have a backbone of a polymer comprising units having a 1,2-diol or 1,3-diol structure, such as polyhydroxy polymers. For example, polyvinyl alcohol (PVA) or copolymers of vinyl alcohol contain a 1,3-diol skeleton. The backbone can also contain hydroxyl groups in the form of 1,2-glycols, such as copolymer units of 1,2-dihydroxyethylene. These can be obtained, for example, by alkaline hydrolysis of vinyl acetate-vinylene carbonate copolymers. Other polymeric diols can be used, such as saccharides.

In addition, the macromers can also contain small proportions, for example, up to 20%, preferably up to 5%, of comonomer units of ethylene, propylene, acrylamide, methacrylamide, dimethacrylamide, hydroxyethyl methacrylate, alkyl methacrylates, alkyl methacrylates which are substituted by hydrophilic groups, such as hydroxyl, carboxyl or amino groups, methyl acrylate, ethyl acrylate, vinylpyrrolidone, hydroxyethyl acrylate, allyl alcohol, styrene, polyalkylene glycols, or similar comonomers usually used.

Polyvinyl alcohols that can be used as macromer backbones include commercially available PVAs, for example Vinol® 107 from Air Products (MW 22,000 to 31,000, 98 to 98.8% hydrolyzed), Polysciences 4397 (MW 25,000, 98.5% hydrolyzed), BF 14 from Chan Chun, Elvanol® 90-50 from DuPont and UF-120 from Unitika. Other producers are, for example, Nippon Gohsei (Gohsenol®), Monsanto (Gelvatol®), Wacker (Polyviol®), Kuraray, Deriki, and Shin-Etsu. In some cases it is advantageous to use Mowiol® products from Hoechst, in particular those of the 3-83, 4-88, 4-98, 6-88, 6-98, 8-88, 8-98, 10-98, 20-98, 26-88, and 40-88 types.

It is also possible to use copolymers of hydrolyzed or partially hydrolyzed vinyl acetate, which are obtainable, for example, as hydrolyzed ethylene-vinyl acetate (EVA), or vinyl chloride-vinyl acetate, N-vinylpyrrolidone-vinyl acetate, and maleic anhydride-vinyl acetate. If the macromer backbones are, for example, copolymers of vinyl acetate and vinylpyrrolidone, it is again possible to use commercially available copolymers, for example the commercial products available under the name Luviskol® from BASF. Particular examples are Luviskol VA 37 HM, Luviskol VA 37 E and Luviskol VA 28. If the macromer backbones are polyvinyl acetates, Mowilith 30 from Hoechst is particularly suitable.

Polyvinyl alcohols that can be derivatized as described herein preferably have a molecular weight of at least about 2,000. As an upper limit, the PVA may have a molecular

weight of up to 1,000,000. Preferably, the PVA has a molecular weight of up to 300,000, especially up to approximately 130,000, and especially preferably up to approximately 60,000.

The PVA usually has a poly(2-hydroxy)ethylene structure. The PVA derivatized in accordance with the disclosure may, however, also comprise hydroxy groups in the form of 1,2-glycols.

The PVA system can be a fully hydrolyzed PVA, with all repeating groups being $-CH_2-CH(OH)$, or a partially hydrolyzed PVA with varying proportions (1% to 25%) of pendant ester groups. PVA with pendant ester groups have repeating groups of the structure $CH_2-CH(OR)$ where R is $COCH_3$ group or longer alkyls, as long as the water solubility of the PVA is preserved. The ester groups can also be substituted by acetaldehyde or butyraldehyde acetals that impart a certain degree of hydrophobicity and strength to the PVA. For an application that requires an oxidatively stable PVA, the commercially available PVA can be broken down by $NaIO_4$-$KMnO_4$ oxidation to yield a small molecular weight (2000 to 4000) PVA.

The PVA is prepared by basic or acidic, partial or virtually complete hydrolysis of polyvinyl acetate. In a preferred embodiment, the PVA comprises less than 50% of vinyl acetate units, especially less than about 25% of vinyl acetate units. Preferred amounts of residual acetate units in the PVA, based on the sum of vinyl alcohol units and acetate units, are approximately from 3 to 25%.

Crosslinkable Groups

The macromers have at least two pendant chains containing groups that can be crosslinked. The term group includes single polymerizable moieties, such as an acrylate, as well as larger crosslinkable regions, such as oligomeric or polymeric regions. The crosslinkers are desirably present in an amount of from approximately 0.01 to 10 milliequivalents of crosslinker per gram of backbone (meq/g), more desirably about 0.05 to 1.5 meq/g. The macromers can contain more than one type of crosslinkable group.

The pendant chains are attached via the hydroxyl groups of the polymer backbone. Desirably, the pendant chains having crosslinkable groups are attached via cyclic acetal linkages to the 1,2-diol or 1,3-diol hydroxyl groups.

Crosslinking of the macromers may be via any of a number of means, such as physical crosslinking or chemical crosslinking. Physical crosslinking includes, but is not limited to, complexation, hydrogen bonding, desolvation, Van der wals interactions, and ionic bonding. Chemical crosslinking can be accomplished by a number of means including, but not limited to, chain reaction (addition) polymerization, step reaction (condensation) polymerization and other methods of increasing the molecular weight of polymers/oligomers to very high molecular weights. Chain reaction polymerization includes, but is not limited to, free radical

polymerization (thermal, photo, redox, atom transfer polymerization, etc.), cationic polymerization (including onium), anionic polymerization (including group transfer polymerization), certain types of coordination polymerization, certain types of ring opening and metathesis polymerizations, etc. Step reaction polymerizations include all polymerizations which follow step growth kinetics including but not limited to reactions of nucleophiles with electrophiles, certain types of coordination polymerization, certain types of ring opening and metathesis polymerizations, etc. Other methods of increasing molecular weight of polymers/oligomers include but are not limited to polyelectrolyte formation, grafting, ionic crosslinking, etc.

Various crosslinkable groups are known to those skilled in the art and can be used, according to what type of crosslinking is desired. For example, hydrogels can be formed by the ionic interaction of divalent cationic metal ions (such as Ca^{+2} and Mg^{+2}) with ionic polysaccharides such as alginates, xanthan gums, natural gum, agar, agarose, carrageenan, fucoidan, furcellaran, laminaran, hypnea, eucheuma, gum arabic, gum ghatti, gum karaya, gum tragacanth, locust beam gum, arabinogalactan, pectin, and amylopectin. Multifunctional cationic polymers, such as poly(l-lysine), poly(allylamine), poly(ethyleneimine), poly(guanidine), poly(vinyl amine), which contain a plurality of amine functionalities along the backbone, may be used to further induce ionic crosslinks.

Hydrophobic interactions are often able to induce physical entanglement, especially in polymers, that induces increases in viscosity, precipitation, or gelation of polymeric solutions. Block and graft copolymers of water soluble and insoluble polymers exhibit such effects, for example, poly(oxyethylene)-poly(oxypropylene) block copolymers, copolymers of poly(oxyethylene) with poly(styrene), poly(caprolactone), poly(butadiene), etc.

Solutions of other synthetic polymers such as poly(N-alkylacrylamides) also form hydrogels that exhibit thermoreversible behavior and exhibit weak physical crosslinks on warming. A two component aqueous solution system may be selected so that the first component (among other components) consists of poly(acrylic acid) or poly(methacrylic acid) at an elevated pH of around 8-9 and the other component consists of (among other components) a solution of poly(ethylene glycol) at an acidic pH, such that the two solutions on being combined in situ result in an immediate increase in viscosity due to physical crosslinking.

Other means for polymerization of the macromers also may be advantageously used with macromers that contain groups that demonstrate activity towards functional groups such as amines, imines, thiols, carboxyls, isocyanates, urethanes, amides, thiocyanates, hydroxyls, etc., which may be naturally present in, on, or around tissue. Alternatively, such functional groups optionally may be provided in some of the macromers of the composition. In this case, no

external initiators of polymerization are needed and polymerization proceeds spontaneously when two complementary reactive functional groups containing moieties interact at the application site.

Desirable crosslinkable groups include (meth)acrylamide, (meth)acrylate, styryl, vinyl ester, vinyl ketone, vinyl ethers, etc. Particularly desirable are ethylenically unsaturated functional groups.

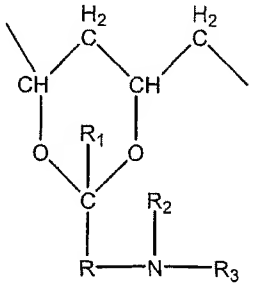
Ethylenically unsaturated groups can be crosslinked via free radical initiated polymerization, including via photoinitiation, redox initiation, and thermal initiation. Systems employing these means of initiation are well known to those skilled in the art. In one embodiment, a two part redox system is employed. One part of the system contains a reducing agent such as a ferrous salt. Various ferrous salts can be used, such as, for example, ferrous gluconate dihydrate, ferrous lactate dihydrate, or ferrous acetate. The other half of the solution contains an oxidizing agent such as hydrogen peroxide. Either or both of the redox solutions can contain macromer, or it may be in a third solution. The two solutions are combined to initiate the crosslinking.

Other reducing agents can be used, such as, but not limited to, cuprous salts, cerous salts, cobaltous salts, permanganate, and manganous salts. Ascorbate, for example, can be used as a coreductant to recycle the reductant and reduce the amount needed. This can reduce the toxicity of a ferrous based system. Other oxidizing agents that can be used include, but are not limited to, t-butyl hydroperoxide, t-butyl peroxide, benzoyl peroxide, cumyl peroxide, etc.

Specific Macromers

Specific macromers that are suitable for use in the compositions are disclosed in U.S. Patent Nos. 5,508,317, 5,665,840, 5,807,927, 5,849,841, 5,932,674, 5,939,489, and 6,011,077.

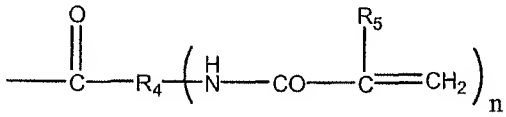
In one embodiment, units containing a crosslinkable group conform, in particular, to the formula I



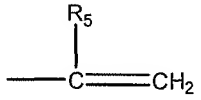
in which R is a linear or branched C_1-C_8 alkylene or a linear or branched C_1-C_{12} alkane. Suitable alkylene examples include octylene, hexylene, pentylene, butylene, propylene, ethylene, methylene, 2-propylene, 2-butylene and 3-pentylene. Preferably lower alkylene R has up to 6 and especially preferably up to 4 carbon atoms. The groups ethylene and butylene are especially preferred. Alkanes include, in particular, methane, ethane, n- or isopropane, n-, sec- or tert-butane, n- or isopentane, hexane, heptane, or octane. Preferred groups contain one to four carbon atoms, in particular one carbon atom.

R_1 is hydrogen, a C_1-C_6 alkyl, or a cycloalkyl, for example, methyl, ethyl, propyl or butyl and R_2 is hydrogen or a C_1-C_6 alkyl, for example, methyl, ethyl, propyl or butyl. R_1 and R_2 are preferably each hydrogen.

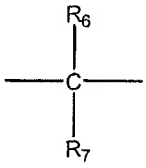
R_3 is an olefinically unsaturated electron attracting copolymerizable radical having up to 25 carbon atoms. In one embodiment, R_3 has the structure



where R_4 is the



group if n=zero, or the



bridge if n=1;

R_5 is hydrogen or C_1-C_4 alkyl, for example, n-butyl, n- or isopropyl, ethyl, or methyl;

n is zero or 1, preferably zero; and

R_6 and R_7, independently of one another, are hydrogen, a linear or branched C_1-C_8 alkyl, aryl or cyclohexyl, for example one of the following: octyl, hexyl, pentyl, butyl, propyl, ethyl,

methyl, 2-propyl, 2-butyl or 3-pentyl. R_6 is preferably hydrogen or the CH_3 group, and R_7 is preferably a C_1-C_4 alkyl group. R_6 and R_7 as aryl are preferably phenyl.

In another embodiment, R_3 is an olefinically unsaturated acyl group of formula R_8-CO-, in which R_8 is an olefinically unsaturated copolymerizable group having from 2 to 24 carbon atoms, preferably from 2 to 8 carbon atoms, especially preferably from 2 to 4 carbon atoms. The olefinically unsaturated copolymerizable radical R_8 having from 2 to 24 carbon atoms is preferably alkenyl having from 2 to 24 carbon atoms, especially alkenyl having from 2 to 8 carbon atoms and especially preferably alkenyl having from 2 to 4 carbon atoms, for example ethenyl, 2-propenyl, 3-propenyl, 2-butenyl, hexenyl, octenyl or dodecenyl. The groups ethenyl and 2-propenyl are preferred, so that the group -CO-R_8 is the acyl radical of acrylic or methacrylic acid.

In another embodiment, the group R_3 is a radical of formula

$$-[CO\text{-}NH\text{-}(R_9\text{-}NH\text{-}CO\text{-}O)_q\text{-}R_{10}\text{-}O]_p\text{-}CO\text{-}R_8$$

wherein p and q are zero or one and

R_9 and R_{10} are each independently lower alkylene having from 2 to 8 carbon atoms, arylene having from 6 to 12 carbon atoms, a saturated divalent cycloaliphatic group having from 6 to 10 carbon atoms, arylenealkylene or alkylenearylene having from 7 to 14 carbon atoms or arylenealkylenearylene having from 13 to 16 carbon atoms, and

R_8 is as defined above.

Lower alkylene R_9 or R_{10} preferably has from 2 to 6 carbon atoms and is especially straight-chained. Suitable examples include propylene, butylene, hexylene, dimethylethylene and, especially preferably, ethylene.

Arylene R_9 or R_{10} is preferably phenylene that is unsubstituted or is substituted by lower alkyl or lower alkoxy, especially 1,3-phenylene or 1,4-phenylene or methyl-1,4-phenylene.

A saturated divalent cycloaliphatic group R_9 or R_{10} is preferably cyclohexylene or cyclohexylene-lower alkylene, for example cyclohexylenemethylene, that is unsubstituted or is substituted by one or more methyl groups, such as, for example, trimethylcyclohexylenemethylene, for example the divalent isophorone radical.

The arylene unit of alkylenearylene or arylenealkylene R_9 or R_{10} is preferably phenylene, unsubstituted or substituted by lower alkyl or lower alkoxy, and the alkylene unit thereof is preferably lower alkylene, such as methylene or ethylene, especially methylene. Such radicals R_9 or R_{10} are therefore preferably phenylenemethylene or methylenephenylene.

Arylenealkylenearylene R_9 or R_{10} is preferably phenylene-lower alkylene-phenylene having up to 4 carbon atoms in the alkylene unit, for example phenyleneethylenephenylene.

The groups R_9 and R_{10} are each independently preferably lower alkylene having from 2 to 6 carbon atoms, phenylene, unsubstituted or substituted by lower alkyl, cyclohexylene or cyclohexylene-lower alkylene, unsubstituted or substituted by lower alkyl, phenylene-lower alkylene, lower alkylene-phenylene or phenylene-lower alkylene-phenylene.

The group -R_9-NH-CO-O- is present when q is one and absent when q is zero. Macromers in which q is zero are preferred.

The group -CO-NH-$(R_9$-NH-CO-O$)_q$-R_{10}-O- is present when p is one and absent when p is zero. Macromers in which p is zero are preferred.

In macromers in which p is one, q is preferably zero. Macromers in which p is one, q is zero, and R_{10} is lower alkylene are especially preferred.

All of the above groups can be monosubstituted or polysubstituted, examples of suitable substituents being the following: C_1-C_4 alkyl, such as methyl, ethyl or propyl, -COOH, -OH, -SH, C_1-C_4 alkoxy (such as methoxy, ethoxy, propoxy, butoxy, or isobutoxy), -NO_2, -NH_2, -NH(C_1-C_4), -NH-CO-NH_2, -N(C_1-C_4 alkyl)$_2$, phenyl (unsubstituted or substituted by, for example, -OH or halogen, such as Cl, Br or especially I), -S(C_1-C_4 alkyl), a 5- or 6-membered heterocyclic ring, such as, in particular, indole or imidazole, -NH-C(NH)-NH_2, phenoxyphenyl (unsubstituted or substituted by, for example, -OH or halogen, such as Cl, Br or especially I), an olefinic group, such as ethylene or vinyl, and CO-NH-C(NH)-NH_2.

Preferred substituents are lower alkyl, which here, as elsewhere in this description, is preferably C_1-C_4 allyl, C_1-C_4 alkoxy, COOH, SH, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$ or halogen. Particular preference is given to C_1-C_4 alkyl, C_1-C_4 alkoxy, COOH and SH.

For the purposes of this invention, cycloalkyl is, in particular, cycloalkyl, and aryl is, in particular, phenyl, unsubstituted or substituted as described above.

Modifiers

The macromers can include further modifier groups and crosslinkable groups. Some such groups are described in U.S. Patent Nos. 5,508,317, 5,665,840, 5,807,927, 5,849,841, 5,932,674, 5,939,489, and 6,011,077. Crosslinkable groups and the optional further modifier groups can be bonded to the macromer backbone in various ways, for example through a certain percentage of the 1,3-diol units being modified to give a 1,3-dioxane, which contains a crosslinkable group, or a further modifier, in the 2-position. Modifiers that might be attached to the backbone include those to modify the hydrophobicity, active agents or groups to allow attachment of active agents, photoinitiators, modifiers to enhance or reduce adhesiveness, modifiers to impart thermoresponsiveness, modifiers to impart other types of responsiveness, modifiers to promote targeting of the drug delivery devices, and additional crosslinking groups.

These modifiers may be attached to the hydroxyl groups in the backbone, or to other monomeric units included in the backbone.

Attaching a cellular adhesion promoter to the macromers can enhance cellular attachment or adhesiveness of the drug delivery implants formed by the compositions. These agents are well known to those skilled in the art and include carboxymethyl dextran, proteoglycans, collagen, gelatin, glucosaminoglycans, fibronectin, lectins, polycations, and natural or synthetic biological cell adhesion agents such as RGD peptides.

Having pendant ester groups that are substituted by acetaldehyde or butyraldehyde acetals, for example, can increase the hydrophobicity of the macromers and the formed hydrogel. Hydrophobic groups can desirably be present in an amount from about 0 to 25%.

It may also be desirable to include on the macromer a molecule that allows visualization of the formed hydrogel. Examples include dyes and molecules visualizable by magnetic resonance imaging.

Degradable Regions

The macromers can form a hydrogel that is degradable. Suitable degradable systems are described in the co-owned application WO 01/44307. In the degradable systems described in that application, the macromers include a degradable region in the backbone or on a pendant chain. The degradable region is preferably degradable under in vivo conditions by hydrolysis. The degradable region can be enzymatically degradable. For example, the degradable region may be polymers or oligomers of glycolide, lactide, ε-caprolactone, other hydroxy acids, and other biologically degradable polymers that yield materials that are non-toxic or present as normal metabolites in the body. Preferred poly(α-hydroxy acids) are poly(glycolic acid), poly(DL-lactic acid) and poly(L-lactic acid). Other useful materials include poly(amino acids), poly(anhydrides), poly(orthoesters), poly(phosphazines), and poly(phosphoesters). Polylactones such as poly(ε-caprolactone), poly(ε-caprolactone), poly(δ-valerolactone) and poly(γ-butyrolactone), for example, are also useful. Enzymatically degradable linkages include poly(amino acids), gelatin, chitosan, and carbohydrates. The biodegradable regions may have a degree of polymerization ranging from one up to values that would yield a product that was not substantially water soluble. Thus, monomeric, dimeric, trimeric, oligomeric, and polymeric regions may be used. The biodegradable region could, for example, be a single methacrylate group.

Biodegradable regions can be constructed from polymers or monomers using linkages susceptible to biodegradation, such as ester, acetal, carbonate, peptide, anhydride, orthoester, phosphazine, and phosphoester bonds. The biodegradable regions may be arranged within the

macromers such that the formed hydrogel has a range of degradability, both in terms of extent of degradation, whether complete or partial, and in terms of time to complete or partial degradation.

Synthesis of Macromers

The macromers can be made by general synthetic methods known to those skilled in the art. The specific macromers discussed above can be made as described in U.S. Patent Nos. 5,508,317, 5,665,840, 5,807,927, 5,849,841, 5,932,674, 5,939,489, and 6,011,077.

The specific macromers described above are extraordinarily stable. Spontaneous crosslinking by homopolymerization does not typically occur. The macromers can furthermore be purified in a manner known per se, for example by precipitation with organic solvents, such as acetone, extraction in a suitable solvent, washing, dialysis, filtration, or ultrafiltration. Ultrafiltration is especially preferred. By means of the purification process the macromers can be obtained in extremely pure form, for example in the form of concentrated aqueous solutions that are free, or at least substantially free, from reaction products, such as salts, and from starting materials.

The preferred purification process for the macromers of the invention, ultrafiltration, can be carried out in a manner known per se. It is possible for the ultrafiltration to be carried out repeatedly, for example from two to ten times. Alternatively, the ultrafiltration can be carried out continuously until the selected degree of purity is attained. The selected degree of purity can in principle be as high as desired. A suitable measure for the degree of purity is, for example, the sodium chloride content of the solution, which can be determined simply in a known manner, such as by conductivity measurements.

The macromers are crosslinkable in an extremely effective and controlled manner.

Vinylic Comonomers

The process for polymerization of the macromers may comprise, for example, crosslinking a macromer comprising units of formula I, especially in substantially pure form, that is to say, for example, after single or repeated ultrafiltration, preferably in solution, especially in aqueous solution, in the absence or presence of an additional vinylic comonomer.

The vinylic comonomer may be hydrophilic or hydrophobic, or a mixture of a hydrophobic and a hydrophilic vinylic monomer. Generally, approximately from 0.01 to 80 units of a typical vinylic comonomer react per unit of formula I, especially from 1 to 30 units per unit of formula I, and especially preferably from 5 to 20 units per unit of formula I.

It is also preferable to use a hydrophobic vinylic comonomer or a mixture of a hydrophobic vinylic comonomer with a hydrophilic vinylic comonomer, the mixture comprising at least 50 percent by weight of a hydrophobic vinylic comonomer. In that manner the mechanical properties of the polymer can be improved without the water content falling

substantially. In principle, however, both conventional hydrophobic vinylic comonomers and conventional hydrophilic vinylic comonomers are suitable for copolymerization with the macromer.

Suitable hydrophobic vinylic comonomers include, without the list being exhaustive, C_1-C_{18} alkyl acrylates and methacrylates, C_3-C_{18} alkyl acrylamides and methacrylamides, acrylonitrile, methacrylonitrile, vinyl-C_1-C_{18} alkanoates, C_2-C_{18} alkenes, C_2-C_{18} haloalkenes, styrene, C_1-C_6 alkylstyrene, vinyl alkyl ethers, in which the alkyl moiety contains from 1 to 6 carbon atoms, C_2-C_{10} perfluoroalkyl acrylates and methacrylates or correspondingly partially fluorinated acrylates and methacrylates, C_3-C_{12} perfluoroalkyl-ethylthiocarbonylaminoethyl acrylates and methacrylates, acryloxy- and methacryloxy-alkylsiloxanes, N-vinylcarbazole, C_3-C_{12} alkyl esters of maleic acid, fumaric acid, itaconic acid, mesaconic acid and the like. C_1-C_4 alkyl esters of vinylically unsaturated carboxylic acids having from 3 to 5 carbon atoms or vinyl esters of carboxylic acids having up to 5 carbon atoms, for example, are preferred.

Examples of suitable hydrophobic vinylic comonomers include methyl acrylate, ethyl acrylate, propyl acrylate, isopropyl acrylate, cyclohexyl acrylate, 2-ethylhexyl acrylate, methyl methacrylate, ethyl methacrylate, propyl methacrylate, vinyl acetate, vinyl propionate, vinyl butyrate, vinyl valerate, styrene, chloroprene, vinyl chloride, vinylidene chloride, acrylonitrile, 1-butene, butadiene, methacrylonitrile, vinyltoluene, vinyl ethyl ether, perfluorohexylethylthiocarbonylaminoethyl methacrylate, isobornyl methacrylate, trifluoroethyl methacrylate, hexafluoroisopropyl methacrylate, hexafluorobutyl methacrylate, tris-trimethylsilyloxy-silyl-propyl methacrylate, 3-methacryloxypropylpentamethyldisiloxane and bis(methacryloxypropyl)tetramethyldisiloxane.

Suitable hydrophilic vinylic comonomers include, without the list being exhaustive, hydroxy-substituted lower alkyl acrylates and methacrylates, acrylamide, methacrylamide, lower alkyl acrylamides and methacrylamides, ethoxylated acrylates and methacrylates, hydroxy-substituted lower alkyl acrylamides and methacrylamides, hydroxy-substituted lower alkyl vinyl ethers, sodium ethylenesulfonate, sodium styrenesulfonate, 2-acrylamido-2-methylpropanesulfonic acid (AMPS® monomer from Lubrizol Corporation), N-vinylpyrrole, N-vinylsuccinimide, N-vinylpyrrolidone, 2- or 4-vinylpyridine, acrylic acid, methacrylic acid, amino- (the term "amino" also including quaternary ammonium), mono-lower alkylamino- or di-lower alkylamino-lower alkyl acrylates and methacrylates, allyl alcohol and the like. Hydroxy-substituted C_2 -C_4 alkyl(meth)acrylates, five- to seven-membered N-vinyl lactams, N,N-di-C_1 -C_4 alkyl(meth)acrylamides and vinylically unsaturated carboxylic acids having a total of from 3 to 5 carbon atoms, for example, are preferred.

Active Agents

An effective amount of one or more biologically active agents is included in the composition and delivered from the formed hydrogel. A wide variety of active agents can be incorporated into the hydrogel. Release of the incorporated additive from the hydrogel is achieved by diffusion of the agent from the hydrogel, degradation of the hydrogel, and/or degradation of a chemical link coupling the agent to the polymer. In this context, an "effective amount" refers to the amount of active agent required to obtain the desired effect.

Biologically active agents that can be delivered using the compositions include prophylactic, therapeutic, and diagnostic agents including naturally occurring agents, synthetic organic molecules, inorganic molecules (collectively referred to herein as an "active agent" or "drug"). Naturally occurring agents include cells, proteins, peptides, carbohydrates, lipids, and nucleic acids. Active agents also include antibiotics, antineoplastic agents, local anesthetics, antiangiogenic agents, vasoactive agents, anticoagulants, immunomodulators, cytotoxic agents, antiviral agents, antibodies, neurotransmitters, psychoactive drugs, and radiation delivery devices, such as radioactive seeds for brachytherapy.

In one preferred embodiment, the active agent is one or more chemotherapeutic agents, such as 5-fluorouracil, cisplatin, adriamycin, or mitamycin. Natural and recombinant peptides and proteins can be delivered, such as, but not limited to, hormones, growth factors, angiogenesis inhibitors, angiogenesis activators, and antibodies. Nucleic acids that can be incorporated include genes, cDNAs encoding proteins, expression vectors, antisense molecules that bind to complementary nucleic acid sequences to inhibit transcription or translation, and ribozymes. For example, genes for the treatment of diseases such as cystic fibrosis can be administered. Polysaccharides, such as heparin, can also be administered.

Exemplary diagnostic agents include gases and other commercially available imaging agents that are used in positron emission tomography (PET), computer assisted tomography (CAT), single photon emission computerized tomography, X-ray, fluoroscopy, and magnetic resonance imaging (MRI). Suitable materials for use as contrast agents in MRI include gadolinium chelates, as well as iron, magnesium, manganese, copper and chromium chelates. Examples of materials useful for CAT and X-rays include iodine based materials.

Cells can be incorporated into the compositions, including cells to encourage tissue growth or cells to secrete a desired active agent. For example, cells that can be incorporated include fibroblasts, endothelial cells, muscle cells, stem cells, etc. Cells can be modified to secrete active agents such as growth factors.

Active agents can be incorporated into the liquid compositions simply by mixing the agent with the composition prior to or upon administration. The active agent will then be entrapped in the hydrogel that is formed upon administration of the composition. The active

agent can be in compound form or can be in the form of degradable or nondegradable nano or microspheres. It some cases, it may be possible and desirable to attach the active agent to the macromer. The active agent may be released from the macromer or hydrogel over time or in response to an environmental condition. The active may be attached by a degradable linkage, such as a linkage susceptible to degradation via hydrolysis or enzymatic degradation. The linkage may be one which is susceptible to degradation at a certain pH, for example. The active agent can be encapsulated in liposomes, which are then entrapped in the hydrogel.

The only limitation as to how much active agent(s) can be loaded into the compositions is one of functionality, namely, the drug load may be increased until the crosslinking of the macromers is adversely affected to an unacceptable degree, or until the properties of the formulation are adversely affected to such a degree as to make administration of the formulation unacceptably difficult. Generally speaking, it is anticipated that in most instances the active agent will make up between about 0.01 to 20% by weight of the formulation with ranges of between about 0.01 to 10% being highly common. These ranges of drug loading are not limiting to the invention. Provided functionality is maintained, drug loadings outside of these ranges fall within the scope of the invention.

Contrast Agents

It may be desirable to include a contrast agent in the compositions. A contrast agent is a biocompatible (non-toxic) material capable of being monitored by, for example, radiography. The contrast agent can be water soluble or water insoluble. Examples of water soluble contrast agents include metrizamide, iopamidol, iothalamate sodium, iodomide sodium, and meglumine. Iodinated liquid contrast agents include Omnipaque®, Visipaque®, and Hypaque-76®. Examples of water insoluble contrast agents are tantalum, tantalum oxide, barium sulfate, gold, tungsten, and platinum. These are commonly available as particles preferably having a size of about 10 μm or less.

The contrast agent can be added to the composition prior to administration. Both solid and liquid contrast agents can be simply mixed with a solution of the liquid compositions or with the solid articles. Liquid contrast agent can be mixed at a concentration of about 10 to 80 volume percent, more desirably about 20 to 50 volume percent. Solid contrast agents are desirably added in an amount of about 10 to 40 weight percent, more preferably about 20 to 40 weight percent.

Other Additives

It may be desirable to include a peroxide stabilizer in redox initiated systems. Examples of peroxide stabilizers are Dequest® products from Solutia Inc., such as for example Dequest® 2010 and Dequest® 2060S. These are phosphonates and chelants that offer stabilization of

peroxide systems. Dequest® 2060S is diethylenetriamine penta(methylene phosphonic acid). These can be added in amounts as recommended by the manufacturer.

It may be desirable to include fillers in the compositions, such as fillers that leach out of the formed hydrogel over a period of time and cause the hydrogel to become porous. Appropriate fillers include calcium salts, for example.

It may be desirable to include one or more pharmaceutically acceptable excipients available in the art. Excipients may be selected that can, in some applications, enhance stability of a protein drug. The excipient may be, e.g., human serum albumin (HSA), bulking agents such as carbohydrates, amino acids, peptides, pH adjusters or buffers, and salts. Additional excipients include zinc, ascorbic acid, mannitol, sucrose, trehalose, cyclodextrans, polyethylene glycol, and other commonly used pharmaceutical excipients, including those described in The United States Pharmacopeia, published by the United States Pharmacopeia Convention, Inc., 1995 (see, e.g., pp. 2205-2207). Exemplary carbohydrates include monosaccharides, such as galactose, and disaccharides such as lactose.

In some cases, the excipients are used as carriers; i.e., they are used to modulate the release rate of the active substances. For example, mannitol can be used to accelerate or delay release.

Fillers, excipients, carriers, and other ingredients that may be added to affect release characteristics or enhance stability, or for any other reason are referred to herein as additives. Additives can be included in the composition by being mixed in or by being attached to the macromer itself.

Characteristics That Can Be Modified

The compositions are highly versatile. A number of characteristics can be easily modified, making the compositions suitable for a number of applications. For example, as discussed above, the polymer backbones can include comonomers to add desired properties, such as, for example, thermoresponsiveness, degradability, gelation speed, and hydrophobicity. Modifiers can be attached to the polymer backbone (or to pendant groups) to add desired properties, such as, for example, thermoresponsiveness, degradability, hydrophobicity, and adhesiveness. Active agents can also be attached to the polymer backbone using the free hydroxyl groups, or can be attached to pendant groups.

The gelation time of the liquid compositions can be varied from about 0.5 seconds to as long as 10 minutes, and longer if desired. The desired gelation time will depend upon whether it is desired to form a plug near the catheter or syringe tip or to form a more diffuse network.

The gelation time will generally be affected by, and can be modified by changing at least the following variables: the initiator system, crosslinker density, macromer molecular weight,

macromer concentration (solids content), and type of crosslinker. A higher crosslinker density will provide faster gelation time; a lower molecular weight will provide a slower gelation time. A higher solids content will provide faster gelation time. For redox systems the gelation time can be designed by varying the concentrations of the redox components. Higher reductant and higher oxidant will provide faster gelation, higher buffer concentration and lower pH will provide faster gelation.

The firmness of the formed hydrogel will be determined in part by the hydrophilic/ hydrophobic balance, where a higher hydrophobic percent provides a firmer hydrogel. The firmness will also be determined by the crosslinker density (higher density provides a firmer hydrogel), the macromer molecular weight (lower MW provides a firmer hydrogel), and the length of the crosslinker (a shorter crosslinker provides a firmer hydrogel).

The swelling of the hydrogel is inversely proportional to the crosslinker density. Generally, no or minimal swelling is desired, desirably less than about 10 percent.

Elasticity of the formed hydrogel can be increased by increasing the size of the backbone between crosslinks and decreasing the crosslinker density. Incomplete crosslinking will also provide a more elastic hydrogel. Preferably the elasticity of the hydrogel substantially matches the elasticity of the tissue to which the composition is to administered.

II. Methods of Using the Compositions

According to the general method, an effective amount of the composition in an aqueous solvent is administered to the site where active agent is needed. The composition includes the macromers, the active agent(s), initiators, if needed, and other desired components. The term "effective amount", as used herein, means the quantity of composition needed to deliver the active agent for the effective period of time. The effective amount of composition administered to a particular patient will vary depending upon a number of factors, including the sex, weight, age, and general health of the patient, the type, concentration, and consistency of the macromers and the hydrogel that results from crosslinking, and the particular site and condition being treated, as well as the effective dosage of the active agent. The composition may be administered over a number of treatment sessions.

The method of using the compositions involves combining the components, including the macromers, the active agent(s), any comonomers, and other additives, under conditions suitable for crosslinking of the macromers. The crosslinking is suitably carried out in a solvent. A suitable solvent is in principle any solvent that dissolves the macromers, for example water, alcohols, such as lower alkanols, for example ethanol or methanol, also carboxylic acid amides, such as dimethylformamide, or dimethyl sulfoxide, and also a mixture of suitable solvents, such as, for example, a mixture of water with an alcohol, such as, for example, a water/ethanol or a

water/methanol mixture. The combination of the macromers is preferably carried out in a substantially aqueous solution. In accordance with the invention, the criterion that the macromer is soluble in water denotes in particular that the macromer is soluble in a concentration of approximately from 3 to 90 percent by weight, preferably approximately from 5 to 60 percent by weight, in a substantially aqueous solution. Insofar as it is possible in an individual case, macromer concentrations of more than 90 percent are also included in accordance with the invention.

Within the scope of this invention, substantially aqueous solutions of the macromer comprise especially solutions of the macromer in water, in aqueous salt solutions, especially in aqueous solutions that have an osmolarity of approximately from 200 to 450 milliosmol per 1000 ml (mOsm/l), preferably an osmolarity of approximately from 250 to 350 mOsm/l, especially approximately 300 mOsm/l, or in mixtures of water or aqueous salt solutions with physiologically tolerable polar organic solvents, such as, for example, glycerol. Solutions of the macromer in water or in aqueous salt solutions are preferred.

The viscosity of the solution of the macromer in the substantially aqueous solution is, within wide limits, not critical, but the solution should preferably be a flowable solution that can be delivered through an appropriately sized catheter or syringe.

In one embodiment, the macromers are crosslinkable via free radical polymerization. A crosslinking initiator is mixed with the macromer solution before administration, during administration, or after administration. For example, a redox system can be mixed with the macromer solution at the time of administration. In one embodiment, the crosslinking initiator may be present at the site of administration. For example, the initiator could be a substance, such as charged blood components, present at the site. Macromers can be used that crosslink when they contact each other. These can be mixed before, during, or after administration. In one embodiment, the crosslinking initiator is an applied stimulus, such as light or heat, which causes crosslinking. Suitable initiators are known for thermal, photo, pH, and redox initiated polymerization. In a redox initiated system employing ferrous ion, peroxide, and ascorbate, the desired amounts of the components will be determined by concerns related to gelation speed, toxicity, extent of gelation desired, and stability. Very generally, the concentration of iron will be about 20 to 2000 ppm; the concentration of hydrogen peroxide will be about 10 to 2000 ppm; the pH will be about 3 to 7; the buffer concentration will be about 10 to 400 mM; and ascorbate concentration will be about 10 to 100 mM.

It may be desirable, if initiator is added to the composition before administration, to use a system that provides delayed crosslinking so that the composition does not gel too early.

Moreover, using delayed curing, the composition can assume or be formed into a desired shape before complete curing has occurred.

In some embodiments, the composition should be injected before substantial crosslinking of the macromers has occurred. This allows the macromers to continue crosslinking in situ and prevents blockage of the syringe needle or catheter with gelled polymer. In addition, such in situ crosslinking may allow anchoring of the hydrogel to host tissue by covalently bonding with collagen molecules present within the host tissue.

Since the compositions preferably comprise no undesired low-molecular-weight constituents, the crosslinked hydrogel products also comprise no such constituents. The implants obtainable by the compositions are therefore distinguished, in an advantageous embodiment, by the fact that they are extremely clean.

Delivery Devices

The compositions can be delivered to the intended site of implantation using delivery devices generally known to those skilled in the art. In most cases, a catheter or syringe is used.

In many cases, a dual syringe having a mixing chamber is used to deliver the liquid composition. A syringe, for example, can be used to deliver the composition containing one or more chemotherapeutic agents directly into a tumor, such as a tumor of the spine, or a brain tumor.

In many cases, a multi-lumen catheter is used to deliver the liquid composition to the intended site of administration. Generally, a two or three lumen catheter will be used, wherein the components of the composition which crosslink or initiate crosslinking are maintained in separate lumens until the time of administration. For example, in the case of a macromer that crosslinks via redox initiated free radical polymerization, one solution containing the reducing agent is delivered through a first lumen while a solution containing the oxidizing agent is delivered through a second lumen. The macromer can be in one or both of the solutions. A third lumen can be used to deliver contrast agent or the contrast agent can be in either or both of the redox solutions. A guidewire can be inserted through any of the lumens, and removed prior to delivery of a solution through that lumen.

In one embodiment, the catheter includes a mixing chamber at its delivery tip. A side by side "double D" lumen can be used, wherein the interior wall has been removed at the distal end to form an area where the two solutions combine before they are injected into the lumen or void. Alternatively, a coaxial catheter can be used, where one of the inner or outer lumens extends further than the other. Other types of multi-lumen catheters are disclosed in the art.

Modifications and variations of the present invention will be apparent to those skilled in the art from the forgoing detailed description. All modifications and variations are intended to

be encompassed by the following claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety.

What is claimed is:

1. A composition for drug delivery comprising macromers having a polymeric backbone comprising units with a 1,2-diol or 1,3-diol structure and at least two pendant chains bearing crosslinkable groups, wherein the macromers can be crosslinked to form a hydrogel.

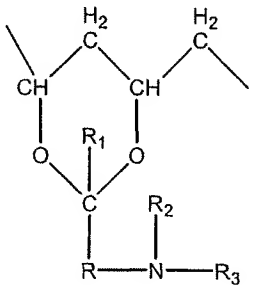
2. The composition of claim 1, wherein the polymer is a polyhydroxy polymer.

3. The composition of claim 2, wherein the pendant chains bearing crosslinkable groups are attached to the backbone via the 1,2-diol or 1,3-diol groups.

4. The composition of claim 3, wherein the pendant chains bearing crosslinkable groups are attached to the backbone via cyclic acetal linkages.

5. The composition of claim 1, wherein the backbone polymer comprises poly(vinyl alcohol) (PVA) and copolymers thereof.

6. The composition of claim 1, wherein the macromer comprises units having the formula:



in which R is a linear or branched C_1-C_8 alkylene or a linear or branched C_1-C_{12} alkane; R_1 is hydrogen, a C_1-C_6 alkyl, or a cycloalkyl; R_2 is hydrogen or a C_1-C_6 alkyl; and R_3 is an olefinically unsaturated electron attracting copolymerizable radical having up to 25 carbon atoms.

7. The composition of claim 1, wherein the macromer further comprises pendant modifier groups.

8. The composition of claim 1, further comprising an active agent.

9. The composition of claim 8, wherein the active agent is attached to the macromer with a cleavable linkage.

10. The composition of claim 9, wherein the linkage to the active agent is cleavable by hydrolysis or enzymatic cleavage.

11. The composition of claim 9, wherein the linkage to the active agent is cleavable in response to a stimulus.

12. The composition of claim 1, wherein the macromers form a hydrogel that is biodegradable.

13. The composition of claim 1, wherein the crosslinkable groups are crosslinkable via free radical polymerization.

14. The composition of claim 12, wherein the crosslinkable groups are olefinically unsaturated groups.

15. A composition for drug delivery comprising macromers that can be crosslinked in situ to form a hydrogel, wherein the macromers have a polymeric backbone comprising units with a 1,2-diol or 1,3-diol structure and at least two pendant chains bearing groups that are crosslinkable via redox initiated free radical polymerization, wherein the composition comprises a first component comprising a reductant and a second component comprising an oxidant wherein the macromers are present in either or both components.

16. The composition of claim 15, further comprising an active agent.

17. The composition of claim 16, wherein the active agent is attached to the macromer with a cleavable linkage.

18. The composition of claim 16, wherein the linkage to the active agent is cleavable by hydrolysis or enzymatic cleavage.

19. The composition of claim 16, wherein the linkage to the active agent is cleavable in response to a stimulus.

20. A method for delivery of an active agent to a site in a body, comprising the steps:

providing a composition comprising macromers having a polymeric backbone comprising units with a 1,2-diol or 1,3-diol structure and at least two pendant chains bearing crosslinkable groups;

providing an active agent:

delivering the composition to the intended site; and

crosslinking the macromers to form a hydrogel that releases the active agent over a period of time.

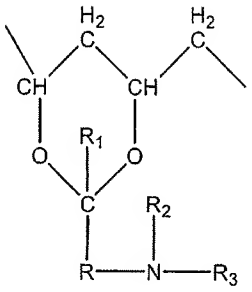
21. The method of claim 20, wherein the polymeric backbone comprises a polyhydroxy polymer.

22. The method of claim 20, wherein the pendant chains bearing crosslinkable groups are attached to the backbone via the 1,2-diol or 1,3-diol groups.

23. The method of claim 20, wherein the pendant chains bearing crosslinkable groups are attached to the backbone via cyclic acetal linkages.

24. The method of claim 20, wherein the polymer comprises poly(vinyl alcohol) (PVA) and copolymers thereof.

25. The method of claim 20, wherein the macromer comprises units having the formula:



in which R is a linear or branched C_1-C_8 alkylene or a linear or branched C_1-C_{12} alkane; R_1 is hydrogen, a C_1-C_6 alkyl, or a cycloalkyl; R_2 is hydrogen or a C_1-C_6 alkyl; and R_3 is an olefinically unsaturated electron attracting copolymerizable radical having up to 25 carbon atoms.

26. The method of claim 20, wherein the macromer further comprises pendant modifier groups.

27. The method of claim 20, wherein the active agent is attached to the macromer with a cleavable linkage.

28. The method of claim 20, wherein the linkage to the active agent is cleavable by hydrolysis or enzymatic cleavage.

29. The method of claim 20, wherein the linkage to the active agent is cleavable in response to a stimulus.

30. The method of claim 20, wherein the active agent is encapsulated in the hydrogel and the hydrogel releases the agent over a period of time ranging from about 1 day to 6 months.

31. The method of claim 20, wherein the hydrogel is biodegradable.

32. The method of claim 20, wherein the macromers are crosslinked via redox initiated free radical polymerization and the composition comprises a first component comprising a reductant and a second component comprising an oxidant wherein the macromers are present in either or both components.

INTERNATIONAL SEARCH REPORT

Inter al Application No
PCT/US 01/28809

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L31/10 A61L31/16 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C08F A61L A61K A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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P,X	WO 01 44307 A (BIOCURE INC) 21 June 2001 (2001-06-21) cited in the application claims --- -/--	1-32

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 March 2002	20/03/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Thornton, S

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INTERNATIONAL SEARCH REPORT

Interr al Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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E	WO 01 68721 A (ASFAW BRUKTAWIT T ;BIOCURE INC (US); CHAOUK HASSAN (US); GOUPIL DE) 20 September 2001 (2001-09-20) claims	1-32

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

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